

JC05 Rec'd PCT/PTO 28 MAR 2002

FORM PTO-1390 (REV 10-94)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER 13357.4USWO
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371				U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) concurrent 10/089431
INTERNATIONAL APPLICATION NO. PCT/JP00/06815	INTERNATIONAL FILING DATE September 29, 2000	PRIORITY DATE CLAIMED October 13, 1999		
TITLE OF INVENTION OPHTHALMIC ADHESIVE PREPARATIONS FOR PERCUTANEOUS ABSORPTION				
APPLICANT(S) FOR DO/EO/US TOJO et al.				
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:				
<ol style="list-style-type: none"> <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. <input checked="" type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(I). <input type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) <ol style="list-style-type: none"> <input checked="" type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau). <input checked="" type="checkbox"/> has been transmitted by the International Bureau. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US) <input checked="" type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)). <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) <ol style="list-style-type: none"> <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau). <input type="checkbox"/> have been transmitted by the International Bureau. <input checked="" type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. <input type="checkbox"/> have not been made and will not be made. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)) <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)). <input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)). 				
Items 11. to 16. below concern document(s) or information included:				
11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.				
12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.				
13. <input checked="" type="checkbox"/> A FIRST preliminary amendment, and Markup copy of the changes made. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment.				
14. <input type="checkbox"/> A substitute specification.				
15. <input type="checkbox"/> A change of power of attorney and/or address letter.				
16. <input checked="" type="checkbox"/> Other items or information: Form PCT/IB/338; Form PCT/IB/308, Form PCT/IB/304; International Search Report.				

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

10/089431

Applicant: TOJO et al.

JC05 Rec'd PCT/PTO 28 MAR 2002

Docket: 13357.4USWO

Title: OPTHALMIC ADHESIVE PREPARATIONS FOR PERCUTANEAOUS ABSORPTION

CERTIFICATE UNDER 37 CFR 1.10

'Express Mail' mailing label number EL669944315US

Date of Deposit March 28, 2002

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By:

Name Chris Stodahl

BOX PATENT APPLICATION

Commissioner for Patents
Washington, D.C. 20231

Sir:

We are transmitting herewith the attached:

- ☒ Transmittal sheet, in duplicate, containing Certificate under 37 CFR 1.10.
- ☒ National Stage PCT Patent Application: Spec. 25 pgs; 20 claims; Abstract 1 pgs.
The fee has been calculated as shown below in the 'Claims as Filed' table.
- ☒ 7 sheets of formal drawings
- ☒ A signed Combined Declaration and Power of Attorney
- ☒ A check in the amount of \$890.00 to cover the Filing Fee
- ☒ Application Data Sheet, 3 pages.
- ☒ Other: Preliminary Amendment, and Markup copy of the changes made; Form PCT/IB/338; Form PCT/IB/308; Form PCT/IB/304; International Search Report.
- ☒ Return postcard

CLAIMS AS FILED

Number of Claims Filed		In Excess of:		Number Extra		Rate		Fee
Basic Filing Fee								\$890.00.00
Total Claims								
20	-	20	=	0	x	18.00	=	\$0.00
Independent Claims								
2	-	3	=	0	x	84.00	=	\$0.00
MULTIPLE DEPENDENT CLAIM FEE								\$0.00
TOTAL FILING FEE								\$890.00

Please charge any additional fees or credit overpayment to Deposit Account No. 13-2725. A duplicate of this sheet is enclosed.

MERCHANT & GOULD P.C.
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(612) 332-5300

By:

Name: Douglas P. Mueller
Reg. No.: 30,300
Initials: D. Mueller:hb



(PTO TRANSMITTAL - NEW FILING)

VERIFICATION OF A TRANSLATION

I, the below named translator, hereby declare that:

My name and post office address are as stated below;


That I am knowledgeable in the English language and in the language in which the below identified Japanese patent application was filed, and that I believe the English translation of the application is a true and complete translation of the application as filed:

Japanese Patent Application No. 291002/99

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: March 22, 2002

Full name of the translator Takumi Hayasaka

Signature of the translator 

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10/089431
JC10 Rec'd PCT/PTO 28 MAR 2002

S/N unknown

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	TOJO et al.	Docket No.:	13357.4USWO
Serial No.:	unknown	Filed:	concurrent herewith
Int'l Appln No.:	PCTJP0006815	Int'l Filing Date:	September 29, 2000
Title:	OPHTHALMIC ADHESIVE PREPARATIONS FOR PERCUTANEAUS ABSORPTION		

CERTIFICATE UNDER 37 CFR 1.10

'Express Mail' mailing label number: EL669944315US

Date of Deposit: March 28, 2002

I hereby certify that this correspondence is being deposited with the United States Postal Service 'Express Mail Post Office To Addressee' service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

By 

Name: Chris Stordahl

PRELIMINARY AMENDMENT

Box PCT
Assistant Commissioner for Patents
Washington, D. C. 20231

Dear Sir:

In connection with the above-identified application filed herewith, please enter the following preliminary amendment.

IN THE ABSTRACT

Insert the attached Abstract page into the application as the last page thereof.

IN THE SPECIFICATION

A courtesy copy of the present specification is enclosed herewith. However, the World Intellectual Property Office (WIPO) copy should be relied upon if it is already in the U.S. Patent Office.

IN THE CLAIMS

Please amend claims 3-9 to read as follows:

3.(amended) The transdermal patch of claim 1 wherein the percutaneous absorption enhancer is polyoxyethylene oleyl ether and/or isopropyl myristate.

4.(amended) The ophthalmic transdermal patch of claim 1 wherein the content of polyoxyethylene oleyl ether in the drug-containing layer is 5-30 W/W%.

5.(amended) The ophthalmic transdermal patch of claim 3 wherein the content of isopropyl myristate in the drug-containing layer is 5-30 W/W%.

6.(amended) The ophthalmic transdermal patch of claim 1 wherein the base matrix comprises acrylic adhesive, silicone elastomer or styrene-isoprene-styrene copolymer.

7.(amended) The ophthalmic transdermal patch of claim 3 wherein the ratio of the content by weight concentration (W/W%) of polyoxyethylene oleyl ether to isopropyl myristate is in the range of 1:0.1-1:5 in the drug-containing layer.

8.(amended) The ophthalmic transdermal patch of claim 1 wherein the drug is a steroidal drug.

9.(amended) The ophthalmic transdermal patch of claim 1 wherein the drug is a compound of the formula (1)

REMARKS

The above preliminary amendment is made to remove multiple dependencies from claims 3-9.

A new abstract page is supplied to conform to that appearing on the publication page of the WIPO application, but the new Abstract is typed on a separate page as required by U.S. practice.

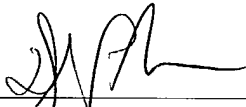
Applicants respectfully request that the preliminary amendment described herein be entered into the record prior to calculation of the filing fee and prior to examination and consideration of the above-identified application.

If a telephone conference would be helpful in resolving any issues concerning this communication, please contact Applicants' primary attorney-of record, Douglas P. Mueller (Reg. No. 30,300), at (612) 371.5237.

Respectfully submitted,

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Dated: March 28, 2002

By 
Douglas P. Mueller
Reg. No. 30,300

DPM:hb

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	TOJO et al.	Docket No.:	13357.4USWO
Serial No.:	unknown	Filed:	concurrent herewith
Int'l Appln No.:	PCTJP0006815	Int'l Filing Date:	September 29, 2000
Title:	OPHTHALMIC ADHESIVE PREPARATIONS FOR PERCUTANEAOUS ABSORPTION		

MARKUP COPY SHOWING THE CHANGES MADE

IN THE CLAIMS

Please amend claims 3-9 to read as follows:

3.(amended) The transdermal patch of claim 1 ~~or 2~~ wherein the percutaneous absorption enhancer is polyoxyethylene oleyl ether and/or isopropyl myristate.

4.(amended) The ophthalmic transdermal patch ~~of one of claims 1 to 3~~ wherein the content of polyoxyethylene oleyl ether in the drug-containing layer is 5-30 W/W%.

5.(amended) The ophthalmic transdermal patch ~~of one of claims 1 to 4~~ claim 3 wherein the content of isopropyl myristate in the drug-containing layer is 5-30 W/W%.

6.(amended) The ophthalmic transdermal patch ~~of one of claims 1 to 5~~ wherein the base matrix comprises acrylic adhesive, silicone elastomer or styrene-isoprene-styrene copolymer.

7.(amended) The ophthalmic transdermal patch ~~of one of claims 1 to 6~~ claim 3 wherein the ratio of the content by weight concentration (W/W%) of polyoxyethylene oleyl ether to isopropyl myristate is in the range of 1:0.1-1:5 in the drug-containing layer.

8.(amended) The ophthalmic transdermal patch ~~of one of claims 1 to 7~~ wherein the drug is a steroidal drug.

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28 MAR 2002

— 1 —

DESCRIPTION

OPHTHALMIC TRANSDERMAL PATCHES

5

TECHNICAL FIELD

The present invention relates to ophthalmic transdermal patches for treating diseases of the posterior segment of the eye including the lens, the vitreous body, the choroid, and the retina. More specifically, the present invention relates to ophthalmic transdermal patches comprising predeter-
10 mined one or more percutaneous absorption enhancers for improving transfer of a drug to ophthalmic tissues.

BACKGROUND ART

After administration of a drug in the form of eye drops or by
15 subconjunctival injection, the concentration of the drug generally would reach, relatively with ease, therapeutically effective levels in the anterior segment of the eye including the cornea and the anterior aqueous humor. However, in tissues in the posterior segment of the eye, including the lens, the vitreous humor, the choroid and the retina, which are located in deeper
20 sites of the eye, the concentration of a drug generally would hardly, or almost never, reach therapeutically effective levels after its topical application either in the form of eye drops or by subconjunctival injection. Therefore, for diseases of the posterior segment of the eye, there have been tried different ways for administration of drugs, such as oral administration, intravenous
25 drip, intravitreal injection or intravitreal implant, in order to deliver the drug to tissues of the posterior segment of the eye. For example, in clinical studies of aldose reductase inhibitors for treating diabetic retinopathy and of immunosuppressant cyclosporine for treating uveitis accompanying Behçet's disease, oral route has been employed to administer those drugs.
30 Ganciclovir, for example, which has been clinically applied as a therapeutic for cytomegalovirus infection of the uvea and the retina, has been administered by intravenous drip or in the form of an intravitreal implant. Furthermore, inhibitors of fibrosis such as triamcinolone acetonide,

5-fluorouracil and mitomycin C have been studied as therapeutics for proliferative vitreoretinopathy, by the method of direct injection into the vitreous body.

However, for oral administration, those drugs generally must be taken
5 several times a day, which would cause a concern about the patients' poor compliance. As to intravenous drip or intravitreous injection, on the other hand, indispensable frequent visit to the doctors would be a burden on the patients. Furthermore, with intravenous drip, there is a risk of causing side effects such as renal or hepatic disorders. Direct intravitreous injection
10 could cause intravitreous hemorrhage or could damage the retina. Intravitreous implants need a surgical operation, which would impose a burden on the patients and present risks entailed in a surgery.

As a system for administering a drug without imposing such a burden on patients, transdermal pharmaceutical preparations of estradiol and
15 nicotine have been on the market. However, as for pharmaceutical preparations aimed to treat diseases localized in the eye by administering a drug through the skin, there is found only a report of a pilocarpine-containing transdermal preparation, which showed an intraocular pressure lowering effect comparable to that of pilocarpine eye drops (Japanese Laid-open Patent
20 Application H8-509716). As a drug that has been used in the form of eye drops for inducing miosis to treat a specific type of glaucoma, pilocarpine is not required to act on the posterior segment of the eye. No attempt has been known before to deliver a drug to the posterior segment of the eye by making use of percutaneous absorption of the drug.

25 On this background, the objective of the present invention is to provide pharmaceutical preparations for delivering a drug to the posterior segment of the eye, that can eliminate the burden on the patients of frequent visit to the doctors or of a surgical operation, and that will make it easier to achieve improved patients' compliance.

30

DISCLOSURE OF INVENTION

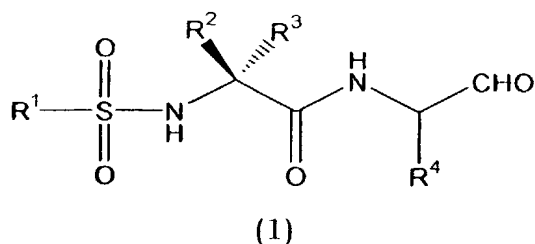
Using drugs that, in light of their pharmacological effect, are desired to act on the very affected site of the posterior segment of the eye, the present

inventors studied the transferability of the drugs to the eye by applying on the skin a base matrix containing them together with different compounds. As a result, the inventors found that the drugs can be delivered to the eye through the skin in other part of the body by enhancing percutaneous
 5 absorption of the drugs by utilizing certain proper compounds, and that polyoxyethylene oleyl ether and isopropyl myristate are particularly preferred percutaneous absorption enhancers for this purpose.

Thus, the present invention provides an ophthalmic transdermal patch for treating diseases of the posterior segment of the eye comprising a
 10 drug-containing layer uniformly containing in a base matrix a percutaneous absorption enhancer and a drug to be delivered to at least a part of the posterior segment of the eye including the lens, the vitreous body, the choroid and the retina.

The present invention further provides a method for treating a disease
 15 of at least a part of the posterior segment of the eye including the lens, the vitreous body, the choroid and the retina, in an animal, particularly a mammalian animal, and inter alia a human, wherein the method comprises applying to the animal an transdermal patch comprising a drug-containing layer uniformly containing in a base matrix an effective amount of a drug to
 20 be delivered to the part and a percutaneous absorption enhancer.

Examples of the drugs used in the present invention include, but are not limited to, anti-cataract agents, anti-inflammatory agents, anti-viral agents, immunosuppressants, calcium channel antagonists, glutamate receptor antagonists and cysteine protease inhibitors, which in general will
 25 hardly, or almost never, reach the posterior segment of the eye by topical instillation or subconjunctival injection. Specific examples include a variety of steroidal drugs represented by anti-inflammatory steroids, and the compound of the formula (1)



and a pharmaceutically acceptable salt thereof, wherein R¹ denotes C1-C4 alkyl, or C6-C10 aryl which may be substituted, R² and R³ are the same or different from each other and denote hydrogen or C1-C4 alkyl, or are combined to form a C3-C7 ring, and R⁴ denotes aryl, cycloalkyl, or a lower alkyl which may be substituted with an aromatic heterocyclic ring.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 is a schematic side view illustrating application of a piece of skin and a pharmaceutical preparation to one of the cells of a side-by-side type permeation experiment device.

Figure 2 is a graph showing in vitro prednisolone permeation through the skin with pharmaceutical preparations P2-P5.

Figure 3 is a graph showing in vitro prednisolone permeation through the skin with pharmaceutical preparations P6-P8.

Figure 4 is a graph showing in vitro prednisolone permeation through the skin with pharmaceutical preparations P9-P10.

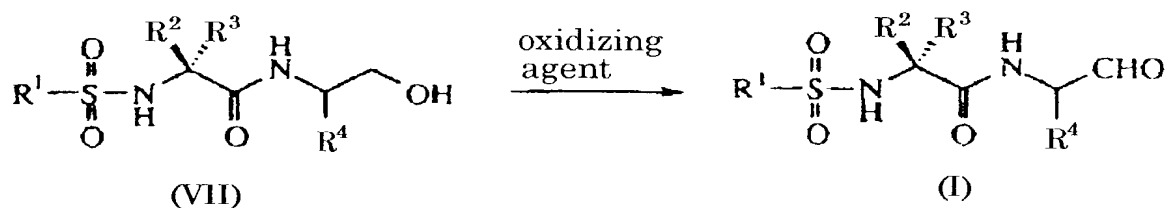
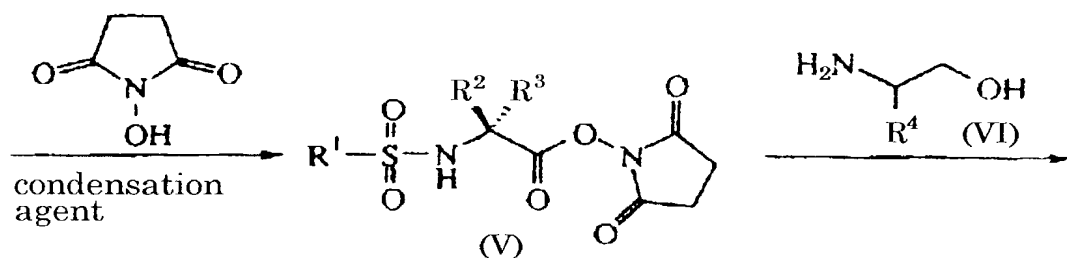
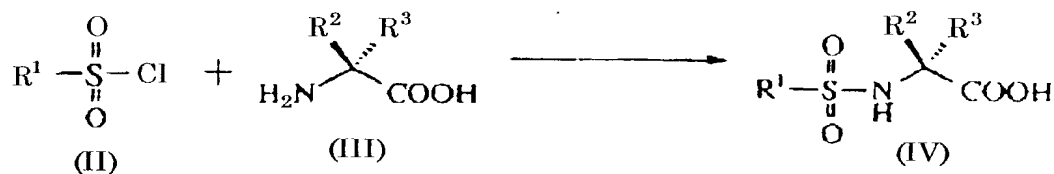
Figure 5 is a graph showing in vitro SJA6017 permeation through the skin with pharmaceutical preparations S2-S4.

Figure 6 is a graph showing the profile of plasma concentration of the drugs after applying pharmaceutical preparations containing prednisolone or SJA6017.

Figure 7 is a schematic illustration of the shape of a SJA6017-containing patch and a rat to which the patch is applied.

BEST MODE FOR CARRYING OUT THE INVENTION

The compound of the formula (1) is described with a number of specific examples of its synthesis and test examples regarding its calpain inhibiting activity and preventive effect on lens opacification in Japanese Laid-open Patent Application No. H10-147564, the entirety of which is incorporated in this application by reference. The compound may be prepared, for example, according to the following reaction scheme, wherein the abbreviations are as defined hereinbefore.



Examples of the sulfonyl chloride represented by the general formula (II) (hereinafter also referred to as "compound (II)") include naphthalenesulfonyl chloride, toluenesulfonyl chloride, fluorobenzenesulfonyl chloride, chlorobenzenesulfonyl chloride, methanesulfonyl chloride, bromobenzenesulfonyl chloride, and benzenesulfonyl chloride.

Examples of the compound represented by the general formula (III) (hereinafter also referred to as "compound (III)") include glycine, alanine, valine, D-valine, norvaline, leucine, isoleucine, norleucine, tert-leucine, 1-aminocyclopropanecarboxylic acid, 1-aminocyclobutanecarboxylic acid, 1-aminocyclopentanecarboxylic acid, and 1-aminocyclohexanecarboxylic acid. The reaction between the compound (II) and the compound (III) may be carried out by well known methods, e.g., Shotten-Bauman reaction and the like.

The condensation of the compound represented by the general

formula (IV) and N-hydroxysuccinimide is carried out in a conventionally employed solvent (e.g. tetrahydrofuran, dichloromethane, chloroform, and ethyl acetate) using a condensation agent. Examples of condensation agents suitable for use include N, N-dicyclohexylcarbodiimide and 1-ethyl-3-(3-
5 dimethylamiopropyl)carbodiimide hydrochloride. Examples of the amino-alcohol represented by the general formula (VI) (hereinafter also referred to as "compound (VI)") include valinol, leucinol, D-leucinol, phenylalaninol, tryptophanol, (S)-2-amino-3-cyclohexyl-1- propanol.

The reaction between the compound represented by the general
10 formula (V) and the compound (VI) is carried out in a solvent such as tetrahydrofuran, dichloromethane, chloroform, ethyl acetate or the like, in the presence of a base (such as triethylamine, pyridine or the like). The compound (I) then may be prepared by oxidizing the compound represented by the general formula (VII) by an oxidizing agent (such as sulfur
15 trioxide-pyridine complex, oxalyl chloride, pyridine chromate or the like). This reaction may be carried out at any desired temperature.

Within the scope of the compound thus obtained, examples of synthesis are described in the aforementioned patent document for the following species.

- 20 (1) N-(2-naphthalenesulfonyl)-L-valyl-L-leucinal,
- (2) N-(4-fluorophenylsulfonyl)-L-valyl-L-leucinal,
- (3) N-(4-chlorophenylsulfonyl)-L-valyl-L-leucinal,
- (4) N-(4-methylphenylsulfonyl)-L-valyl-L-leucinal,
- (5) N-(2-naphthalenesulfonyl)-L-tert-leucyl-L-leucinal,
- 25 (6) N-(4-fluorophenylsulfonyl)-D-valyl-L-leucinal,
- (7) N-(4-fluorophenylsulfonyl)-L-norleucyl-L-leucinal,
- (8) N-(4-fluorophenylsulfonyl)-L-norvalyl-L-leucinal,
- (9) 1-(2-naphthalenesulfonylamino)cyclopentanecarbonyl-L-leucinal,
- (10) N-(2-naphthalenesulfonyl)-L-tert-leucyl-L-phenylalaninal,
- 30 (11) N-(4-fluorophenylsulfonyl)-L-valyl-L-phenylalaninal,
- (12) N-(2-naphthalenesulfonyl)-L-valyl-L-phenylalaninal,
- (13) N-(4-chlorophenylsulfonyl)-L-valyl-L-phenylalaninal,
- (14) N-(4-methylphenylsulfonyl)- L-valyl-L-phenylalaninal,

- (15) 1-(2-naphthalenesulfonylamino)cyclohexanecarbonyl-L-phenylalaninal,
- (16) 1-(2-naphthalenesulfonylamino)cyclopentanecarbonyl-L-phenylalaninal,
- (17) N-(4-chlorophenylsulfonyl)-L-valyl-L-tryptophanal,
- (18) N-(4-fluorophenylsulfonyl)-L-valyl-L-tryptophanal,
- 5 (19) 1-(2-naphthalenesulfonylamino)cyclohexanecarbonyl-L-tryptophanal,
- (20) N-(2-naphthalenesulfonyl)-L-tert-leucyl-L-tryptophanal,
- (21) N-(4-fluorophenylsulfonyl)-L-valyl-L-cyclohexylalaninal,
- (22) N-(2-naphthalenesulfonyl)-L-valyl-cyclohexylalaninal,
- (23) N-(4-chlorophenylsulfonyl)-L-valyl-L-cyclohexylalaninal,
- 10 (24) N-(4-fluorophenylsulfonyl)-D-valyl-D-leucinal,
- (25) N-(4-fluorophenylsulfonyl)-L-valyl-D-leucinal,
- (26) N-(4-fluorophenylsulfonyl)-L-valyl-L-alaninal, and
- (27) N-methylsulfonyl-L-valyl-L-leucinal

In the same patent document, it is also reported that the compound
 15 possesses a cysteine protease inhibitor activity and therefore is useful as a
 drug for prevention or treatment of ischemic diseases, inflammation, cataract,
 retinopathy and the like. In the scope of the compound, examples parti-
 cularly suitable to the purpose of the present invention include N-(4-
 fluorophenylsulfonyl)-L-valyl-L-leucinal or a pharmaceutically acceptable salt
 20 thereof.

In the present invention, especially suitable percutaneous absorption
 enhancers are, as mentioned, polyoxyethylene oleyl ether and isopropyl
 myristate, which may be used alone or in combination. When used alone,
 their content in the drug-containing layer is preferably in the range of 5-30
 25 W/W% for polyoxyethylene oleyl ether, and 5-30 W/W% also for isopropyl
 myristate. Though they may be used in combination as desired, it is
 particularly preferable that the ratio of the content by weight concentration
 (W/W%) of polyoxyethylene oleyl ether to isopropyl myristate falls in the
 range of 1:0.1-1:5 in the drug-containing layer.

30 The content of polyoxyethylene oleyl ether in the drug-containing
 layer is more preferably 10-30 W/W%, still more preferably 10-20 W/W%,
 and most preferably 10-15 W/W%.

The content of isopropyl myristate in the drug-containing layer is

more preferably 10-30 W/W%, still more preferably 10-20 W/W%, and most preferably 10-15 W/W%. Combined use of polyoxyethylene oleyl ether and isopropyl myristate further enhances percutaneous absorption of drugs.

In addition to polyoxyethylene oleyl ether and/or isopropyl myristate,
5 the ophthalmic transdermal patches of the present invention may contain other supplementary percutaneous absorption enhancers known in the art. Examples of such percutaneous absorption enhancers include salts of N-acylsarcosine such as salts (sodium, potassium, magnesium, calcium, aluminum salts or the like) of N-lauroylsarcosine, cocoyl sarcosine,
10 N-stearoylsarcosine, oleoylsarcosine, palmitoylsarcosine and the like, salts of higher fatty acids such as salts (sodium, potassium, magnesium, calcium, aluminum salts or the like) of capric acid, myristic acid, palmitic acid, lauric acid, stearic acid, palmitoleic acid, oleic acid, vaccenic acid, linolic acid, linolenic acid and the like, esters of higher fatty acids such as esters of capric
15 acid, lauric acid, palmitic acid, stearic acid and the like with alcohols (methanol, ethanol, propanol, isopropanol, butanol, hexanol, pentanol, heptaneol and the like), hydroxydicarboxylic acids and dicarboxylic acids such as lactic acid, malic acid, tartaric acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, azelaic
20 acid, sebacic acid, fumaric acid, maleic acid and the like, monoterpenes such as l-menthol, d-limonene and the like, surfactants such as sodium lauryl sulfate, sodium dodecylbenzensulfonate, sodium alkyldiphenylether-disulfonate, dioctyl sulfosuccinates, ammonium polyoxyalkyl phenyl ether sulfate and the like, alcohols such as ethanol, glycerol, diethylene glycol,
25 propylene glycol, polyethylene glycol, higher alcohols and the like, dimethyl sulfoxide, alkyl or methyl derivatives of salicylic acid, urea, dimethylacetamide, dimethylformamide and the like, pyrrolidone derivatives such as polyvinylpyrrolidone, dodecylpyrrolidone, methylpyrrolidone and the like, and liquid vaseline, liquid paraffin, allantoin, squalene, Carbopol,
30 vaseline, gelatin, amino acids, dodecylazacycloheptane-2-one and the like.

The base matrix that is particularly preferable comprises acrylic adhesives, silicone-based elastomers or styrene-isoprene-styrene copolymers, from which one can choose as desired. The matrix may be supported on a

surface of one of supporting materials conventionally used in pharmaceutical preparations applied to the skin such as tapes, patches, poultices and the like, or any other support made of a material that will not affect the use of the present invention.

5 As for acrylic adhesive matrix, for example, acrylic copolymer resin PE-300 (solid content 40 %), a product of NIPPON CARBIDE INDUSTRIES CO., INC., may be used as an adhesive, and CK-401 (solid content 10-15 %), a product of NIPPON CARBIDE INDUSTRIES CO., INC., as a coagulation enhancer.

10 As for silicone-based matrix, for example, SLASTIC® MDX40-4210, a product of DOW CORNING ASIA, may be used as a silicone elastomer, and 360 MEDICAL FLUID, 20 cs, a product of DOW CORNING ASIA, as silicone oil. When providing an adhesive layer on the surface of the drug-containing layer comprising silicone-based matrix, for example, a silicone-based
15 adhesive may be selected as desired from commercially available ones such as BIO-PSAQ7-4501 or BIO-PSAX7-4201, products of DOW CORNING ASIA, polymethylphenylsiloxane copolymer of LINTEC CORPORATION, or acrylic acid-dimethylsiloxane copolymer such as BPK-1, BPK-2 of WAKO PURE CHEMICAL INDUSTRIES, LTD. and the like.

20 As a styrene-isoprene-styrene copolymer, CARIFLEX TR-1107 and CARIFLEX TR-1111 of SHELL CHEMICAL, and JSR5000 of NIHON SYNTHETIC RUBBER are suitably used.

The concentration of the drug contained in the base matrix may be 1-20 W/W%, preferably 2-15 W/W%, and adjusted as desired in accordance
25 with the disease to be treated and its severity.

In the polyoxyethylene oleyl ether used in the present invention, the average number of ethylene oxide added per oleyl moiety is preferably 4.4-5.5, and especially preferably about 5. It can be obtained by reacting oleyl alcohol with ethylene oxide having a hydroxyl group value of 4.5-5.5 as
30 determined by the method described in the section of "Hydroxyl Group Value" in Testing Method for Fats and Oils in the Japanese Pharmacopoeia, 13th ed. For example, NOFABLE EAO-9905 of NOF CORPORATION may be favorably used.

The diseases of the posterior segment of the eye which are treated by the present invention are, for example, diseases of the lens, the vitreous body, the uvea including the choroid, or the retina, such as diabetic cataract, acute retinal necrosis syndrome, cytomegalovirus retinitis, intrinsic uveitis caused
5 by autoimmune mechanism or abnormal immune response, proliferative vitreoretinopathy, diabetic retinopathy, retinal vessel occlusion, retinal periphlebitis, ischemic oculopathy, disorders of retinal vessels such as retinal aneurysm, retinopathy caused by ocular hypertension, nephropathy or hemopathy, retinal pigment epitheliopathy, retinal dystrophy, macular
10 dystrophy, retinochoroidal atrophy, chorioretinopathy, macular dystrophy, macular edema, retinal pigment epithelium detachment, retinal detachment, degenerative retinoschisis, tumors such as retinoblastoma, retinal pigment epithelial tumor and tumor in optic disc capillary, optic neuropathy such as ischemic optic neuropathy, disc swelling such as choked disc and
15 papilledema, open angle glaucoma, low tension glaucoma, angle closure glaucoma and the like.

Examples of drugs used in the present invention include aldose reductase inhibitors, corticosteroids (e.g. prednisolone, triamcinolone acetonide, dexamethasone), anti-viral agents (e.g., acyclovir, ganciclovir),
20 immunosuppressants (e.g., cyclosporine), calcium ion channel antagonists (e.g., flunarizine, nifedipine, nicardipine), glutamate receptor antagonists (e.g., memantine, dizocilpine, dextrometorphan), and cysteine protease inhibitors [e.g., a compound represented by the formula (1), in particular
N-(4-fluorophenylsulfonyl)-L-valyl-L-leucinal].

25 In use, the ophthalmic transdermal patches of the present invention may be applied at any location of the body surface as desired. It may be applied on a site relatively close to the eye, e.g., on the temple or around the eye, in particular on the skin of the eyelids or next to the lateral angle of the eye.

30 [Test Example]

The effect of transdermal patches of the present invention will be described below referring to test examples.

(1) Transdermal patches used

According to the formulas shown in Tables 1 and 2, transdermal patches were prepared containing prednisolone or N-(4-fluorophenylsulfonyl)-L-valyl-L-leucinal (hereinafter also referred to as "SJA6017"), respectively. In the tables, "%" means "W/W%" for the weight of the solid components. The concentration of the drugs (W/W%) were calculated as "drug/(drug + percutaneous absorption enhancers + acrylic adhesive + coagulation enhancer) x 100". EAO9905 indicates polyoxyethylene oleyl ether (NOFABLE EAO-9905: NOF CORPORATION) and IPM indicates isopropyl myristate.

Acrylic copolymer base matrix was prepared from an acrylic adhesive consisting of 40 % acrylate copolymer solution in acetic acid and toluene (PE300: NIPPON CARBIDE INDUSTRIES CO., INC.) and a coagulation enhancer consisting of an approx. 7-10 % cross-linking agent solution in ethyl acetate and toluene (CK401: NIPPON CARBIDE INDUSTRIES CO., INC.), by mixing and reacting the acrylate copolymer and the cross-linking agent at a ratio of 100:1 by weight.

(a) Formula of transdermal patches containing prednisolone

Table 1

Preparation No.	Prednisolone (%)	EAO9905 (%)	IPM (%)	Acrylate copolymer (+ cross-linking agent) (%)
P1 (Control)	3	0	0	97
P2	3	10	10	77
P3	3	10	20	67
P4	3	20	10	67
P5	3	20	20	57
P6	3	5	0	92
P7	3	10	0	87
P8	3	20	0	77
P9	3	0	10	87
P10	3	0	20	77

(b) Formula of transdermal patches containing N-(4-fluorophenylsulfonyl)-L-valyl-L-leucinal

Table 2

Preparation No.	SJA6017 (%)	EAO9905 (%)	IPM (%)	Acrylate copolymer (+ cross-linking agent) (%)
S1 (Control)	5	0	0	95
S2	5	20	0	75
S3	5	20	10	65
S4	5	20	20	55

(2) Device for percutaneous permeation experiment

5 In percutaneous permeation experiment, a side-by-side type cells, PERMCELL HK-5P (KOKURA GLASS KOGYO) was used as the permeation experiment device. Figure 1 illustrates one of its symmetrical pair of cells. The effective area of the opening 2 to the cell 1 is 0.64 cm², and the effective capacity of the cell 1 is 5.0 ml. The water jacket of the device is connected
10 to a circulating thermostatic bath by silicone tubing to keep the temperature of the cell interior at 37°C. The interior of the cell is constantly stirred with a magnetic stirrer (1200 rpm).

(3) Preparation of skin samples

Scratch-free abdominal skin of female hairless mice of 8 to 11-week
15 old (Hr/Kud strain) was cut out and attached fat was removed using anatomical scissors.

(4) Drug permeation experiment using skin samples

Referring to Figure 1, the skin 3 of the hairless mouse obtained above is applied to cover the opening 2 (0.64 cm²) to the cell 1 (used as the receptor
20 cell) of the side-by-side type diffusion cells. A transdermal patch 5 is applied on the skin. In order to keep it on the skin, the patch then is covered with a support net 7, which in turn is covered with an aluminum sheet 9. The other cell is placed over the sheet, with the openings to the cells aligned, and the cells are fixed with a holder. The receptor cell is filled
25 with 40 W/W% PEG400 aqueous solution and kept at 37 °C. At predetermined intervals, 100 μL samples are removed and the amount of the drug transferred to the receptor cell through the skin is determined by

HPLC under the conditions indicated in (6) below. To keep the liquid volume in the receptor cell constant, the same amount of 40 W/W% PEG400 aqueous solution is supplemented after each sampling. Under these conditions, the permeability of the skin to a drug is kept substantially
5 constant for at least 48 hours.

(5) In vivo test-1

Male Wistar/ST rats of 8-week old (body weight approx. 250 g), which had been removed of the hair, were used to examine the transfer of drugs from the transdermal patches to the plasma (prednisolone and SJA6017) and
10 to the ocular tissues (prednisolone). For measuring transfer of the drugs into the plasma, cervical vein cannulation had been performed in advance to allow sampling of the blood over time. The above transdermal patches, No. P5 (prednisolone) and No. S4 (SJA 6017) with the surface area of 10 cm² were applied on the abdominal skin. 0.5-ml blood sampling was performed
15 over time through a sampling port of the cannula placed on the occipital region of the rat's head. For measurement of transfer of the drug to the ocular tissues, rats were euthanized with an excess amount of sodium pentobarbital solution and the ocular tissues were removed. The tissues were pretreated, extracted and measured to determine the concentration of
20 the drug by HPLC.

(6) In vivo test-2

A study of SJA6017-containing transdermal patch according to the formula below was made for examining transfer of SJA6017 from the patch to the plasma and to the ocular tissues, and comparison of the results with
25 those from intravenous injection was also made.

(Formula)

SJA6017	0.15 g (5 W/W%)
EAO9905	0.6 g (20 W/W%)
Isopropyl myristate	0.6g (20 W/W%)
30 Acrylic adhesive (PE-300)	1.6336 g
<u>Coagulation enhancer (CK-401)</u>	<u>0.0016 5 g</u>
Total	3.00 g

Male 9-week old Wistar/ST rats (body weight approx. 280-300 g), which had been removed of the hair, were used for the percutaneous absorption experiment. The hair was removed under anesthesia with a clipper and a shaver carefully to avoid injuring the skin. A SJA6017 transdermal patch having a drug-containing layer according to the above formula with the size of 5.0 x 6.0 cm (30 cm²) was applied to the animals (n=10) of the percutaneous administration group on the abdominal skin and secured in position with a supporting tape to prevent it from falling. After 12 hours of application, the animals were sacrificed and the blood was collected from the abdominal aorta, and the plasma separated. The eyes were excised at the same time. Each of the eyes was separated into the aqueous humor, the lens and the other tissues (consisting of the cornea, the sclera, the iris-ciliary body, the vitreous body and the retina-choroid), and corresponding tissues separated from the 20 eyes were combined, respectively, to make a sample.

An intravenous administration experiment was carried out using 5 male Wistar rats (body weight approx. 600 g: 592 ± 34 g) by administering 2 mg/kg SJA6017 through the tail vein of the animals under pentobarbital anesthesia. For the administration, a solution was used containing 10 mg SJA6017 dissolved in 10 ml mixture of ethanol/PEG400/water (1/2/1). Fifteen minutes after the intravenous administration, the animals were sacrificed, the blood was collected through the abdominal aorta, and the plasma separated. The eyes were excised at the same time. Each of the eyes was separated into the aqueous humor, the lens and the other tissues (consisting of the cornea, the sclera, the iris-ciliary body, the vitreous body and the retina-choroid), and corresponding tissues separated from the 10 eyes were combined, respectively, to make a sample.

(7) Determination of the concentration of the drugs in the samples

(a) Determination of prednisolone concentration

Determination of prednisolone (hereinafter also referred to as "PN") concentration in the samples was carried out by HPLC under the following conditions.

Column: CAPCELL PAK CN UG120 5 μm, 4.6 mm φ × 250 mm

Guard column: CAPCELL PAK CN UG120 5 μ m, 4.6 mm ϕ \times 35 mm

Detection: UV-254 nm

Mobile phase: acetonitrile/water = 30/70

Flow rate: 1.0 ml/min

5 Temperature: 40 $^{\circ}$ C

Injection volume: 50 μ l or 100 μ l

Retention time: approx. 6-7 minutes

(b) Determination of the concentration of N-(4-fluorophenylsulfonyl)-L-valyl-L-leucinal

10 Determination of the concentration of N-(4-fluorophenylsulfonyl)-L-valyl-L-leucinal in the samples was carried out by HPLC under the following conditions.

(i) In vitro test (concentration in the receptor cell)

Column: BECKMAN ULTRASPHERE ODS 5 μ m 2.0 mm ϕ \times 250 mm

15 Detection: UV-250 nm

Mobile phase: 1 % trifluoroacetic acid in a mixture of acetonitrile/water (35/65)

Flow rate: 0.25 ml/min

Temperature: 45 $^{\circ}$ C

20 Injection volume: 100 μ l

Retention time: approx. 16 min

(ii) In vivo test

Column: CAPCELL PAK C₁₈ SG120 5 μ m 4.6 mm ϕ \times 250 mm

Detection: UV-272 nm

25 Mobile phase: 0.02 M phosphate buffer (pH 7):acetonitrile = 45:55

Flow rate: 1.0 ml/min

Temperature: 40 $^{\circ}$ C

Injection volume: 100 μ l

Retention time: approx. 14 min

30 [Test results]

<Test results obtained using percutaneous permeation experiment device>

Tables 3-6 and Figures 2-5 shows accumulative amounts (in μ g/cm²) of prednisolone and N-(4-fluorophenylsulfonyl)-L-valyl-L-leucinal (SJA6017)

transferred into the receptor cell 36 or 42 hours after start of the tests using the percutaneous permeation experiment device.

As shown in Tables 3-5 and Figures 2-4, the percutaneous permeation of prednisolone from the transdermal patches P2-P10, which contained polyoxyethylene oleyl ether and/or isopropyl myristate, was greatly improved compared with the control (P1).

Table 3

Time (hr)	P1 (Control)		P5		P4		P3		P2	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	0.00	0.00	1.27	0.60	0.53	0.12	0.12	0.02	0.16	0.03
3	0.00	0.00	4.33	1.18	1.96	0.50	0.39	0.10	0.51	0.11
6	0.00	0.00	20.21	3.61	9.83	2.17	2.94	0.43	3.23	0.00
9	0.00	0.00	42.64	6.22	21.54	4.56	7.60	1.41	6.82	0.61
12	0.00	0.00	69.04	8.98	32.78	5.46	13.30	1.67	11.18	1.14
18	0.30	0.06	135.47	14.46	59.69	9.70	28.20	3.75	21.72	1.86
24	0.45	0.08	158.94	10.10	86.49	14.76	45.13	5.85	33.56	3.21
30	0.60	0.11	266.44	13.98	144.41	29.40	60.00	4.14	46.51	4.13
36	0.78	0.14	316.72	14.27	166.61	24.41	77.53	6.57	59.92	4.35
42	-	-	348.41	12.21	206.23	35.21	92.59	8.02	72.56	4.97

Table 4

Time (hr)	P1 (Control)		P6		P7		P8	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	0.00	0.00	0.00	0.00	0.00	0.00	0.19	0.08
3	0.00	0.00	0.00	0.00	0.23	0.04	0.55	0.26
6	0.00	0.00	0.57	0.19	1.64	0.50	3.64	1.70
9	0.00	0.00	1.40	0.51	4.18	1.37	8.30	3.73
12	0.00	0.00	2.43	0.79	7.29	2.44	13.51	5.88
18	0.30	0.06	5.21	1.63	14.28	4.95	25.13	10.12
24	0.45	0.08	8.77	2.77	23.15	7.86	37.82	14.79
30	0.60	0.11	11.11	2.65	32.43	10.86	50.68	17.84
36	0.78	0.14	14.87	3.23	42.83	14.86	64.74	21.97
42	-	-	19.92	4.01	53.42	18.84	79.33	24.83

Table 5

Time (hr)	P1 (Control)		P9		P10	
	Mean	SD	Mean	SD	Mean	SD
0	0.00	0.00	0.00	0.00	0.00	0.00
1	0.00	0.00	0.00	0.00	0.00	0.00
2	0.00	0.00	0.00	0.00	0.00	0.00
3	0.00	0.00	0.00	0.00	0.00	0.00
6	0.00	0.00	0.00	0.00	0.57	0.10
9	0.00	0.00	0.73	0.12	1.29	0.17
12	0.00	0.00	1.19	0.19	1.93	0.21
18	0.30	0.06	1.96	0.28	3.26	0.29
24	0.45	0.08	2.51	0.32	4.64	0.39
30	0.60	0.11	3.18	0.40	5.60	1.05
36	0.78	0.14	4.14	0.55	7.66	0.52

As to N-(4-fluorophenylsulfonyl)-L-valyl-L-leucinal, it is shown in Table 5 and Figure 5 that percutaneous permeation was clearly noted with transdermal patches S2-S4 of the present invention while no percutaneous permeation was observed with the control (S1).

Table 6

Time (hr)	S1 (Control)		S2		S3		S4	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
6	0.00	0.00	3.19	0.33	6.15	3.47	4.97	1.47
12	0.00	0.00	9.63	2.04	13.80	7.75	16.65	6.59
18	0.00	0.00	17.16	1.97	26.35	11.87	27.32	11.75
24	0.00	0.00	26.07	2.69	41.14	16.45	39.67	16.12
30	0.00	0.00	33.67	4.81	57.59	20.63	49.68	21.14
36	0.00	0.00	42.83	5.80	78.83	26.75	62.37	25.57
48	0.00	0.00	62.48	8.58	111.32	38.71	88.36	37.86

10

<The results of in vivo test>

(1) Plasma concentration of the drugs after application of transdermal patches (in vivo test-1)

Table 7 below and Figure 6 show the profiles of plasma concentration

of prednisolone and N-(4-fluorophenylsulfonyl)-L-valyl- L-leucinal (SJA6107) after application of the aforementioned transdermal patches (10 cm²) indicated above as Nos. P5 and S5, respectively, which contained one of those drugs, to the skin of the animals. After the application, the plasma concentration of the drugs gradually rose and reached the peaks at 8 and 12 hours after application for prednisolone and SJA6017, respectively. Though the concentration of the drugs gradually lowered afterwards, substantial concentration of the drugs was noted even 24 hours after the application, when SJA6017 concentration, in particular, was still maintained at about 85 % of its peak.

Table 7

Time (hr)	SJA6017			Prednisolone		
	Plasma concentration	SD	n	Plasma concentration	SD	n
0	0	0	5	0	0	5
2	30	5	6	220	233	16
4	36	7	2	288	190	5
6	58	28	6	385	245	15
8	50	19	2	608	344	7
12	114	56	9	148	43	7
18	68	24	4	99	25	4
24	98	8	5	77	30	5

Unit: ng/ml

15 (2) Intraocular concentration of prednisolone (in vivo test-1)

Prednisolone amount was determined in the plasma and the eyeball of the rats to which were applied a 3 % prednisolone-containing preparation, P5. As a result, 70 ng/g prednisolone was detected 6 hours after the application of the preparation. This indicates that prednisolone was transferred to the interior of the eye at a concentration that was equivalent to 18 % of the plasma concentration (Table 8). As all the samples were collected at a time, 6 hours after the application, because it was necessary to combine multiple

eyes for extraction due to the minute amount of ocular tissues, no measurement could be made at any other point.

(3) Plasma and intraocular concentration of SJA6017 (in vivo test-2)

Table 8 shows the concentration of SJA6017 in the eyeball and in the plasma after the application of the SJA6017-containing transdermal patches, in comparison with corresponding values after intravenous administration of SJA6017. Also included in the table are the results of prednisolone transdermal administration in the above in vivo test-1.

10

Table 8

	SJA6017 transdermal application	SJA6017 intravenous injection	Prednisolone transdermal application
Point of measument	12 hourrs after application	15 minutes after intravenous injection	6 hours after application
Plasma concentration [ng/ml]	47 ± 12	120 ± 16	385
Intraocular concentration [ng/g eye]	7.2	16	70
Eyeball/plasma ratio	16 %	13 %	18 %
[Intraocular concentration, itemized]			
Aqueous humor [ng/ml]	not detected	not detected	-
Lens [ng/g tissue]	1.1 (2.3%)*2	not detected	-
Other ocular tissues*1 [ng/g tissues]	13.8 (29.6%)*2	33.4 (27.8%)*2	-

*1 Other ocular tissues: cornea, sclera, iris-ciliary body, vitreous body, retina-choroid

*2 Ratio to plasma concentration (100 %)

15

Table 8 shows that 7.2 ng/g of SJA6017 was detected in the eyeball 12 hours after the application of the SJA6017-containing preparation. This value reaches about 16 % of the plasma concentration of the drug, and is higher than the corresponding value (13 %) detected after intravenous application. This indicates continuous nature of absorption of SJA6017 from the patch and that this method of administration of a drug by transdermal patches is a method available to continuously transfer a drug from the plasma into the eyeball.

20

The drug was detected in other parts of the eyeball than the aqueous humor. Among the parts other than the aqueous humor, drug transfer was higher in the tissues including the iris-ciliary body, the vitreous body, the retina-choroid. These results indicate that a transdermal patch is a suitable
5 form for long-term application of a drug to intraocular tissues.

[Examples]

The present invention is described in further detail with reference to examples. It is not intended, however, that the present invention be limited to the examples.

10 <Example 1> Acrylic patches

Acrylic patches containing 5 W/W% (0.15 g) of a drug (prednisolone or SJA6017) and 30 W/W% (0.9 g) of polyoxyethylene oleyl ether (NOFABLE EAO-9905: NOF CORPORATION) as a percutaneous absorption enhancer in the drug-containing layer were prepared according to the following formula.
15 Briefly, prednisolone and about 1.0 ml of toluene was mixed and sonicated for about 30 seconds in a disposable cup to dissolve or disperse the drug. Polyoxyethylene oleyl ether was added to this and mixed well. Then, 5.0 g of the acrylic adhesive (PE-300: NIPPON CARBIDE INDUSTRIES CO., INC.), which served as a dispersion base, and 0.2 g of the coagulation agent
20 (CK-401: NIPPON CARBIDE INDUSTRIES CO., INC.) were added in this order and mixed well. The mixture was degassed, spread over a release membrane with a doctor knife or a baker applicator (JAPAN APPLIED TECHNOLOGY), and left stand until the organic solvent evaporated. A lining film was placed over this, glued to it with pressure using a roller, and put in
25 a thermostatic chamber at about 40 °C for 8-12 hours to cross-linking to take place.

(Formula)

Drug	0.15 g
Polyoxyethylene oleyl ether	0.9 g
30 Acrylic adhesive (PE-300)	5.0 g
Coagulation enhancer (CK-401)	0.2 g
<u>Toluene</u>	<u>1.0 ml</u>

<Example 2> Acrylic patches

Acrylic patches containing 10 W/W% (0.3 g) of a drug (prednisolone or SJA6017) and 20 W/W% (0.6 g) of polyoxyethylene oleyl ether (NOFABLE EAO-9905: NOF CORPORATION) as a percutaneous absorption enhancer in the drug-containing layer were prepared in the same manner as in Example 1 according to the following formula.

(Formula)

Drug	0.3 g
Polyoxyethylene oleyl ether	0.6 g
10 Acrylic adhesive (PE-300)	5.0 g
Coagulation enhancer (CK-401)	0.2 g
<u>Toluene</u>	<u>1.0 ml</u>

<Example 3> Acrylic patches

15 Acrylic patches containing 15 W/W% (0.45 g) of a drug (prednisolone or SJA6017) and 20 W/W% (0.6 g) of polyoxyethylene oleyl ether (NOFABLE EAO-9905: NOF CORPORATION) as a percutaneous absorption enhancer in the drug-containing layer were prepared in the same manner as in Example 1 according to the following formula.

20 (Formula)

Drug	0.45 g
Polyoxyethylene oleyl ether	0.6 g
Acrylic adhesive (PE-300)	5.0 g
Coagulation enhancer (CK-401)	0.2 g
25 <u>Toluene</u>	<u>1.0 ml</u>

<Example 4> Acrylic patches

Acrylic patches containing 5 W/W% (0.15 g) of a drug (prednisolone or SJA6017), 10 W/W% (0.3 g) of polyoxyethylene oleyl ether (NOFABLE EAO-9905: NOF CORPORATION), and 20 W/W% (0.6 g) isopropyl myristate in the drug-containing layer were prepared in the same manner as in Example 1 according to the following formula.

(Formula)

	Drug	0.15 g
	Polyoxyethylene oleyl ether	0.3 g
	Isopropyl myristate	0.6 g
	Acrylic adhesive (PE-300)	5.0 g
5	Coagulation enhancer (CK-401)	0.2 g
	<u>Toluene</u>	<u>1.0 ml</u>

<Example 5> Acrylic patches

Acrylic patches containing 10 W/W% (0.3 g) of a drug (prednisolone or SJA6017), 20 W/W% (0.6 g) of polyoxyethylene oleyl ether (NOFABLE EAO-9905: NOF CORPORATION), and 10 W/W% (0.3 g) isopropyl myristate in the drug-containing layer were prepared in the same manner as in Example 1 according to the following formula.

(Formula)

15	Drug	0.3 g
	Polyoxyethylene oleyl ether	0.6 g
	Isopropyl myristate	0.3 g
	Acrylic adhesive (PE-300)	5.0 g
	Coagulation enhancer (CK-401)	0.2 g
20.	<u>Toluene</u>	<u>1.0 ml</u>

<Example 6> Silicone-based patches

Silicone-based patches containing 5 W/W% (0.33 g) of a drug (prednisolone or SJA6017) and 20 W/W% (1.34 g) of polyoxyethylene oleyl ether (NOFABLE EAO-9905: NOF CORPORATION) as a percutaneous absorption enhancer in the drug-containing layer were prepared according to the following formula. Briefly, prednisolone and polyoxyethylene oleyl ether were mixed well in a disposable cup and, after addition of about 2.5 ml of ethyl acetate, sonicated for about 30 seconds to dissolve or disperse the drug. To this were added 0.25 g of silicone oil (360 medical fluid, 20 cs: DOW CORNING ASIA), 4.5 g of a silicone elastomer (SLASTIC MDX4-4210, medical grade: DOW CORNING ASIA), and 0.25 g of a curing agent (curing agent for SLASTIC MDX4-4210: DOW CORNING ASIA) in the order and mixed well.

The mixture was degassed, spread over a backing liner (Cerafeel #25) with a doctor knife or a baker applicator (JAPAN APPLIED TECHNOLOGY), left stand for 1 hour at room temperature, allowed to cure at 40 °C, and cut into a predetermined size to give silicone-based transdermal patches.

5 (Formula)

	Drug	0.33 g
	Polyoxyethylene oleyl ether	1.34 g
	Silicone elastomer	4.5 g
	Silicone oil	0.25 g
10	Curing agent	0.25 g
	<u>Ethyl acetate</u>	<u>2.5 ml</u>

<Example 7> Silicone-based patches

15 Silicone-based patches containing 10 W/W% (0.83 g) of a drug (prednisolone or SJA6017) and 30 W/W% (2.5 g) of polyoxyethylene oleyl ether (NOFABLE EAO-9905: NOF CORPORATION) as a percutaneous absorption enhancer in the drug-containing layer were prepared in the same manner as in Example 6 according to the following formula

(Formula)

20	Drug	0.83 g
	Polyoxyethylene oleyl ether	2.5 g
	Silicone elastomer	4.5 g
	Silicone oil	0.25 g
	Curing agent	0.25 g
25	<u>Ethyl acetate</u>	<u>2.5 ml</u>

<Example 8> Silicone-based patches

30 Silicone-based patches containing 10 W/W% (0.83 g) of a drug (prednisolone or SJA6017), 10 W/W% (0.83 g) of polyoxyethylene oleyl ether (NOFABLE EAO-9905: NOF CORPORATION) and 20 W/W% (1.67 g) of isopropyl myristate in the drug-containing layer were prepared in the same manner as in Example 6 according to the following formula.

(Formula)

	Drug	0.83 g
	Polyoxyethylene oleyl ether	0.83 g
	Isopropyl myristate	1.67 g
	Silicone elastomer	4.5 g
5	Silicone oil	0.25 g
	Curing agent	0.25 g
	<u>Ethyl acetate</u>	<u>2.5 ml</u>

<Example 9> Silicone-based patches

10 Silicone-based patches containing 15 W/W% (1.15 g) of a drug (prednisolone or SJA6017), 10 W/W% (0.77 g) of polyoxyethylene oleyl ether (NOFABLE EAO-9905: NOF CORPORATION) and 10 W/W% (0.77 g) of isopropyl myristate in the drug-containing layer were prepared in the same manner as in Example 6 according to the following formula.

15 (Formula)

	Drug	1.15 g
	Polyoxyethylene oleyl ether	0.77 g
	Isopropyl myristate	0.77 g
	Silicone elastomer	4.5 g
20	Silicone oil	0.25 g
	Curing agent	0.25 g
	<u>Ethyl acetate</u>	<u>2.5 ml</u>

<Example 10> Styrene-isoprene-styrene copolymer-based patches

25 Styrene-isoprene-styrene copolymer-based patches containing 5 W/W% (0.15 g) of a drug (prednisolone or SJA6017) and 30 W/W% (0.9 g) of polyoxyethylene oleyl ether (NOFABLE EAO-9905: NOF CORPORATION) as a percutaneous absorption enhancer in the drug-containing layer were prepared according to the following formula. Briefly, 0.9 g of

30 styrene-isoprene-styrene copolymer (CARIFLEX TR-1107: SHELL CHEMICAL) was dissolved in 1.05 g of liquid paraffin at about 100 °C. To this were added the drug and polyoxyethylene oleyl ether and mixed well. The mixture was spread over a backing liner (Cerafeel # 25) with a doctor knife or

a bake applicator (JAPAN APPLIED TECHNOLOGY), and cut into a predetermined size to give styrene-isoprene-styrene copolymer-based transdermal patches.

(Formula)

5	Drug	0.15 g
	Polyoxyethylene oleyl ether	0.9 g
	Styrene-isoprene-styrene copolymer	0.9 g
	<u>Liquid paraffin</u>	<u>0.15 g</u>

10 <Example 11> Styrene-isoprene-styrene copolymer-based patches

Styrene-isoprene-styrene copolymer-based patches containing 5 W/W% (0.15 g) of a drug (prednisolone or SJA6017), 20 W/W% (0.6 g) of polyoxyethylene oleyl ether (NOFABLE EAO-9905: NOF CORPORATION) and 10 W/W% (0.3 g) of isopropyl myristate in the drug-containing layer were prepared in the same manner as in Example 10 according to the following formula.

(Formula)

	Drug	0.15 g
	Polyoxyethylene oleyl ether	0.6 g
20	Isopropyl myristate	0.3 g
	Styrene-isoprene-styrene copolymer	0.9 g
	<u>Liquid paraffin</u>	<u>0.15 g</u>

INDUSTRIAL APPLICABILITY

25 The present invention provides pharmaceutical preparations for administration of drugs for treating diseases of the posterior segment of the eye, which preparation will make it easier to achieve improved patients' compliance, and minimize burden on the patients, and eliminate unnecessary patients' risks.

CLAIMS

1. An ophthalmic transdermal patch for treating diseases of the posterior segment of the eye comprising a drug-containing layer uniformly containing in a base matrix a percutaneous absorption enhancer and a drug to be delivered to at least a part of the posterior segment of the eye including the lens, the vitreous body, the choroid and the retina.

2. The ophthalmic transdermal patch of claim 1 wherein the drug is an anti-cataract agent, an anti-inflammatory agent, an anti-viral agent, an immunosuppressant, a calcium channel antagonist, a glutamate receptor antagonist or a cysteine protease inhibitor.

3. The transdermal patch of claim 1 or 2 wherein the percutaneous absorption enhancer is polyoxyethylene oleyl ether and/or isopropyl myristate.

4. The ophthalmic transdermal patch of one of claims 1 to 3 wherein the content of polyoxyethylene oleyl ether in the drug-containing layer is 5-30 W/W%.

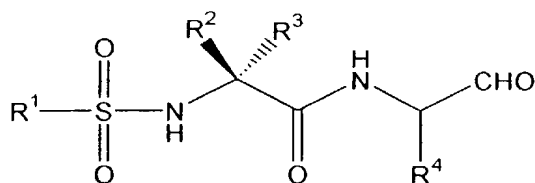
5. The ophthalmic transdermal patch of one of claims 1 to 4 wherein the content of isopropyl myristate in the drug-containing layer is 5-30 W/W%.

6. The ophthalmic transdermal patch of one of claims 1 to 5 wherein the base matrix comprises acrylic adhesive, silicone elastomer or styrene-isoprene-styrene copolymer.

7. The ophthalmic transdermal patch of one of claims 1 to 6 wherein the ratio of the content by weight concentration (W/W%) of polyoxyethylene oleyl ether to isopropyl myristate is in the range of 1:0.1-1:5 in the drug-containing layer.

8. The ophthalmic transdermal patch of one of claims 1 to 7 wherein the drug is a steroidal drug.

9. The ophthalmic transdermal patch of one of claims 1 to 7 wherein the drug is a compound of the formula (1)



(1)

or a pharmaceutically acceptable salt thereof, wherein R¹ denotes C1-C4 alkyl, or C6-C10 aryl which may be substituted, R² and R³ are the same or different from each other and denote hydrogen or C1-C4 alkyl, or are combined to form a C3-C7 ring, and R⁴ denotes aryl, cycloalkyl, or a lower alkyl which may be substituted with an aromatic heterocyclic ring.

10. The ophthalmic transdermal patch of claim 9 wherein the drug is N-(4-fluorophenylsulfonyl)-L-valyl-L-leucinal or a pharmaceutically acceptable salt thereof.

11. A method for treating a disease of at least a part of the posterior segment of the eye including the lens, the vitreous body, the choroid and the retina in an animal including a human, wherein the method comprises applying to the animal a transdermal patch comprising a drug-containing layer uniformly containing in a base matrix an effective amount of a drug to be delivered to the part and a percutaneous absorption enhancer.

12. The method of claim 11 wherein the drug is an anti-cataract agent, an anti-inflammatory agent, an anti-viral agent, an immunosuppressant, a calcium channel antagonist, a glutamate receptor antagonist or a cysteine protease inhibitor.

13. The method of claim 11 wherein the percutaneous absorption enhancer is polyoxyethylene oleyl ether and/or isopropyl myristate.

14. The method of claim 13 wherein the content of polyoxyethylene oleyl ether in the drug-containing layer is 5-30 W/W%.

15. The method of claim 13 wherein the content of isopropyl myristate in the drug-containing layer is 5-30 W/W%.

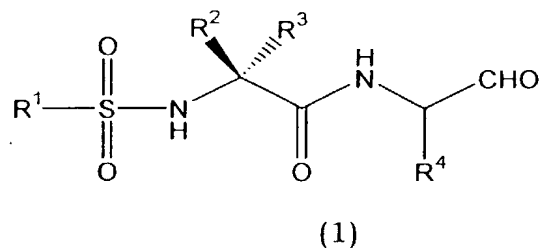
16. The method of claim 11 wherein the base matrix comprises acrylic adhesive, silicone elastomer or styrene-isoprene-styrene copolymer.

17. The method of claim 13 wherein the ratio of the content by

weight concentration (W/W%) of polyoxyethylene oleyl ether to isopropyl myristate is in the range of 1:0.1-1:5 in the drug-containing layer.

18. The method of claim 11 wherein the drug is a steroidal drug.

19. The method of claim 11 wherein the drug is a compound of the formula (1)



or a pharmaceutically acceptable salt thereof, wherein R¹ denotes C1-C4 alkyl, or C6-C10 aryl which may be substituted, R² and R³ are the same or different from each other and denote hydrogen or C1-C4 alkyl, or are combined to form a C3-C7 ring, and R⁴ denotes aryl, cycloalkyl, or a lower alkyl which may be substituted with an aromatic heterocyclic ring.

20. The method of claim 19 wherein the drug is N-(4-fluorophenyl-sulfonyl)-L-valyl-L-leucinal or a pharmaceutically acceptable salt thereof.

2)特許協力条約に基づいて公開された国際

(19) 世界知的所有権機関
国際事務局



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- (81) 指定国 (国内): CA, JP, KR, US.
- (84) 指定国 (広域): ヨーロッパ特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).
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— 国際調査報告書
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(54) Title: OPHTHALMIC ADHESIVE PREPARATIONS FOR PERCUTANEOUS ABSORPTION

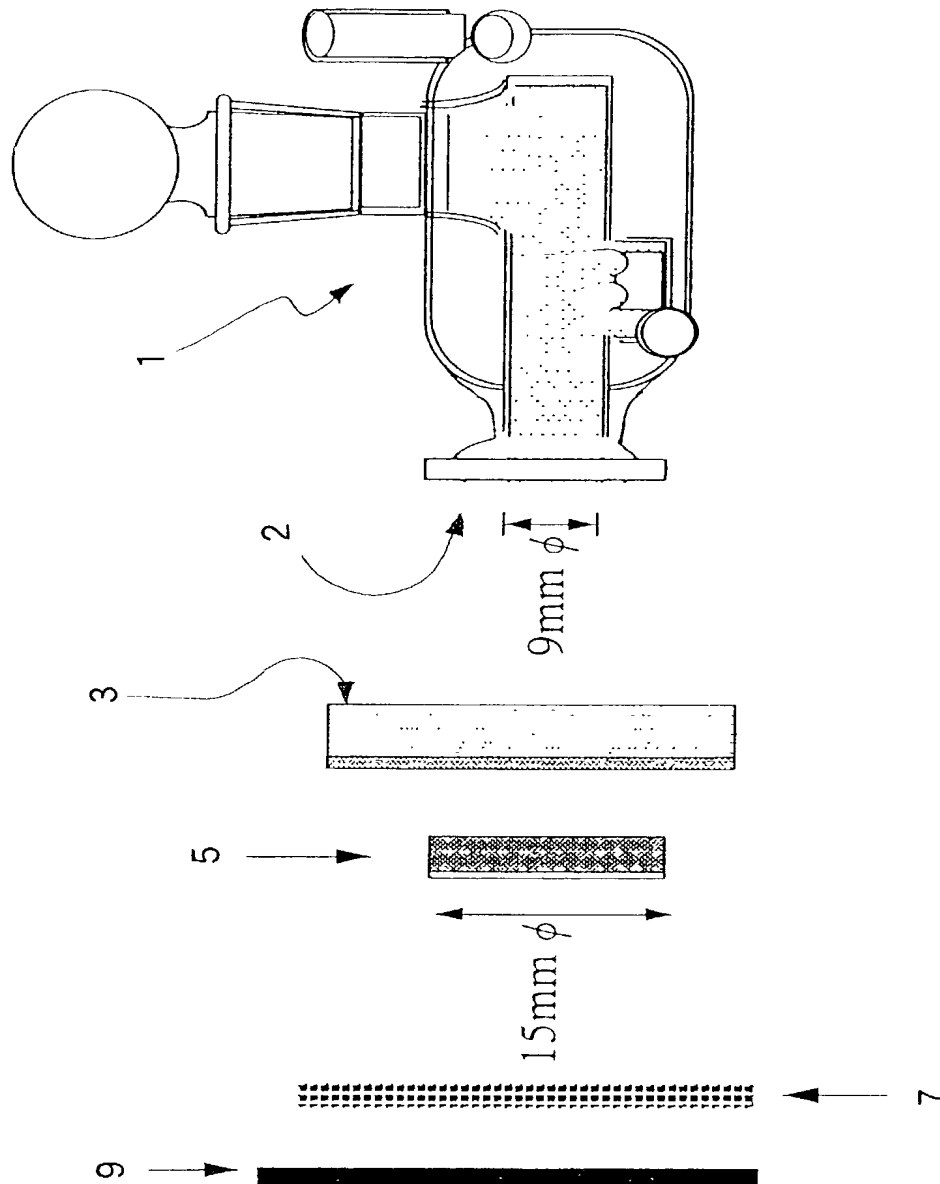
(54) 発明の名称: 眼科用経皮吸収貼付剤

(57) Abstract: Ophthalmic adhesive preparations for percutaneous absorption to be used in treating diseases in the posterior parts of eye characterized by having a drug-containing layer which contains a drug to be delivered to the posterior parts of eye including the crystalline lens, the vitreous body, the uvea and the retina, together with a percutaneous sorbent comprising polyoxyethylene oleyl ether and/or isopropyl myristate uniformly dispersed in a base matrix.

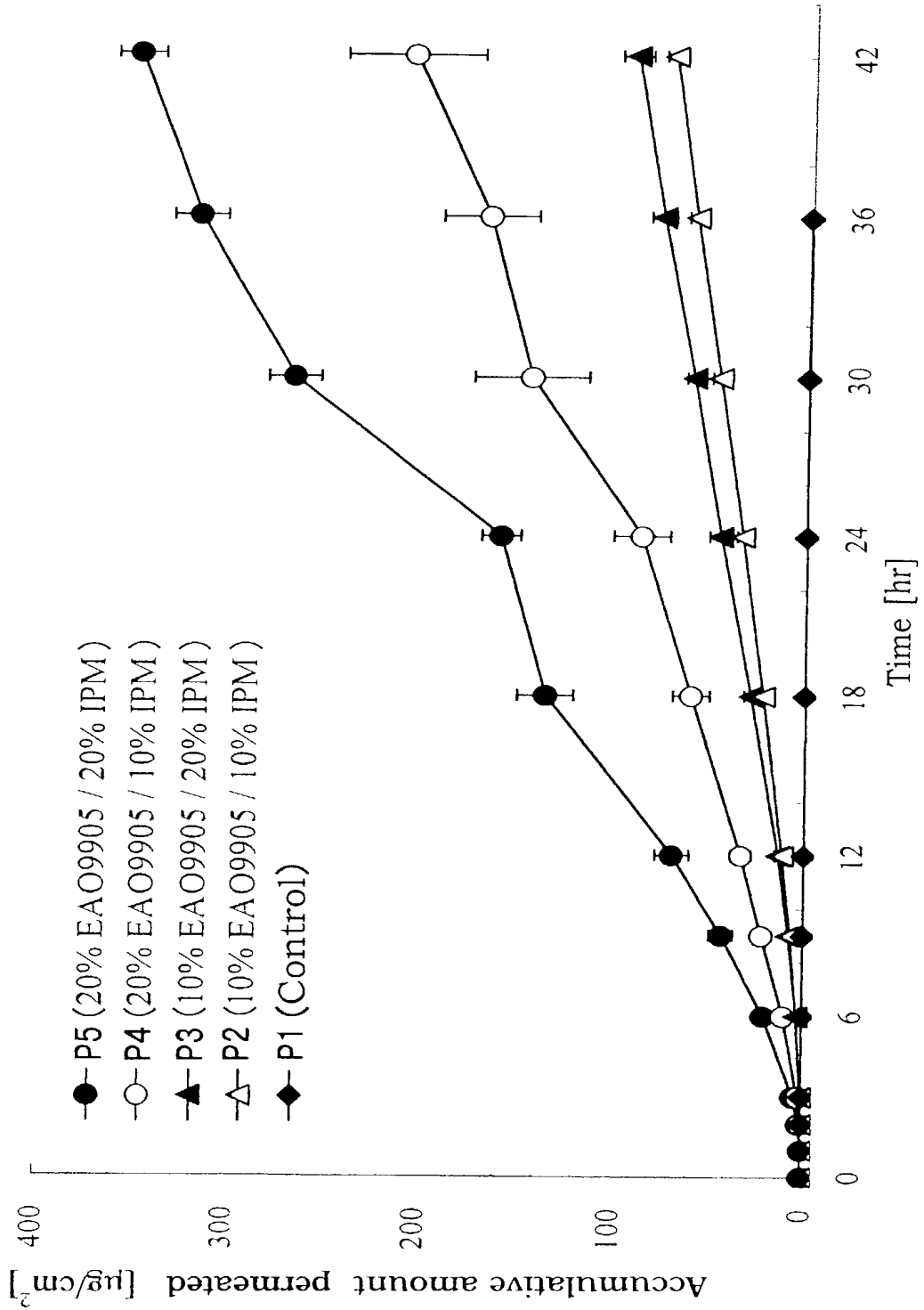
(57) 要約:

水晶体、硝子体、ぶどう膜及び網膜を含んでなる後眼部に対して到達させようとする薬物と、ポリオキシエチレンオレイルエーテル及び／又はミリスチン酸イソプロピルである経皮吸収促進剤を基剤マトリクス中に均質に含有してなる薬物含有層を有することを特徴とする、後眼部の疾患を治療するための眼科用経皮吸収貼付剤が開示されている。

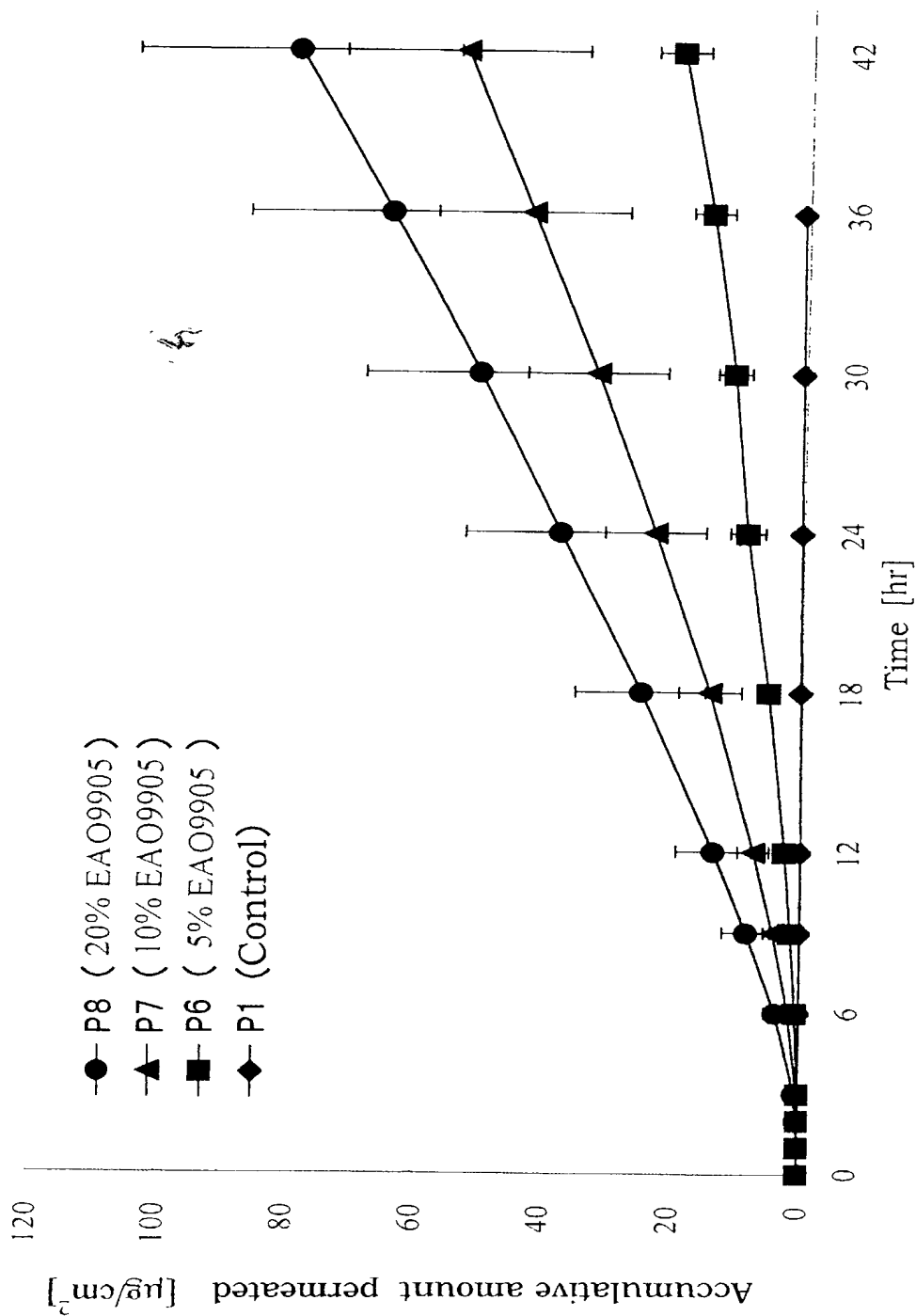
WO 01/26648 A1



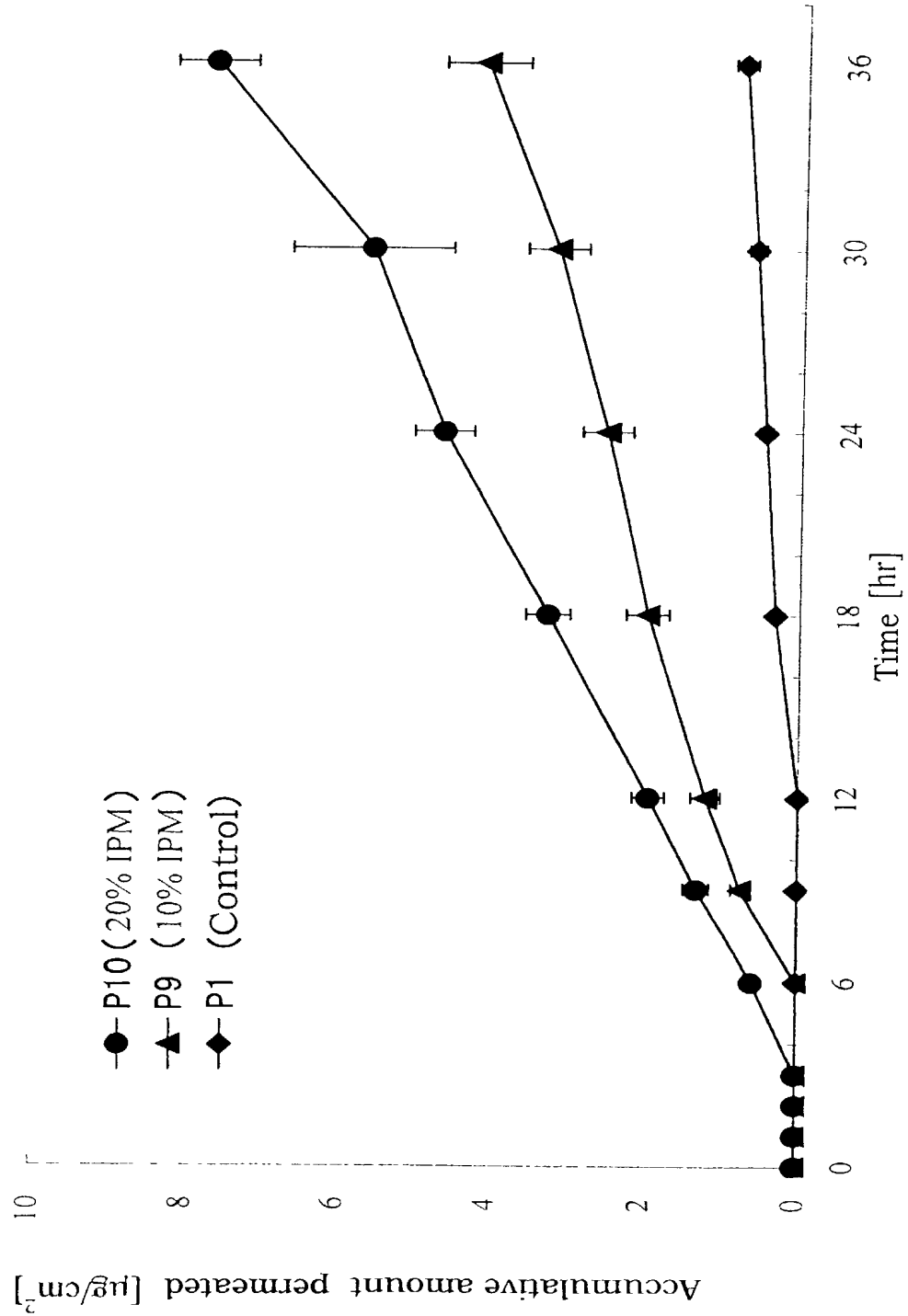
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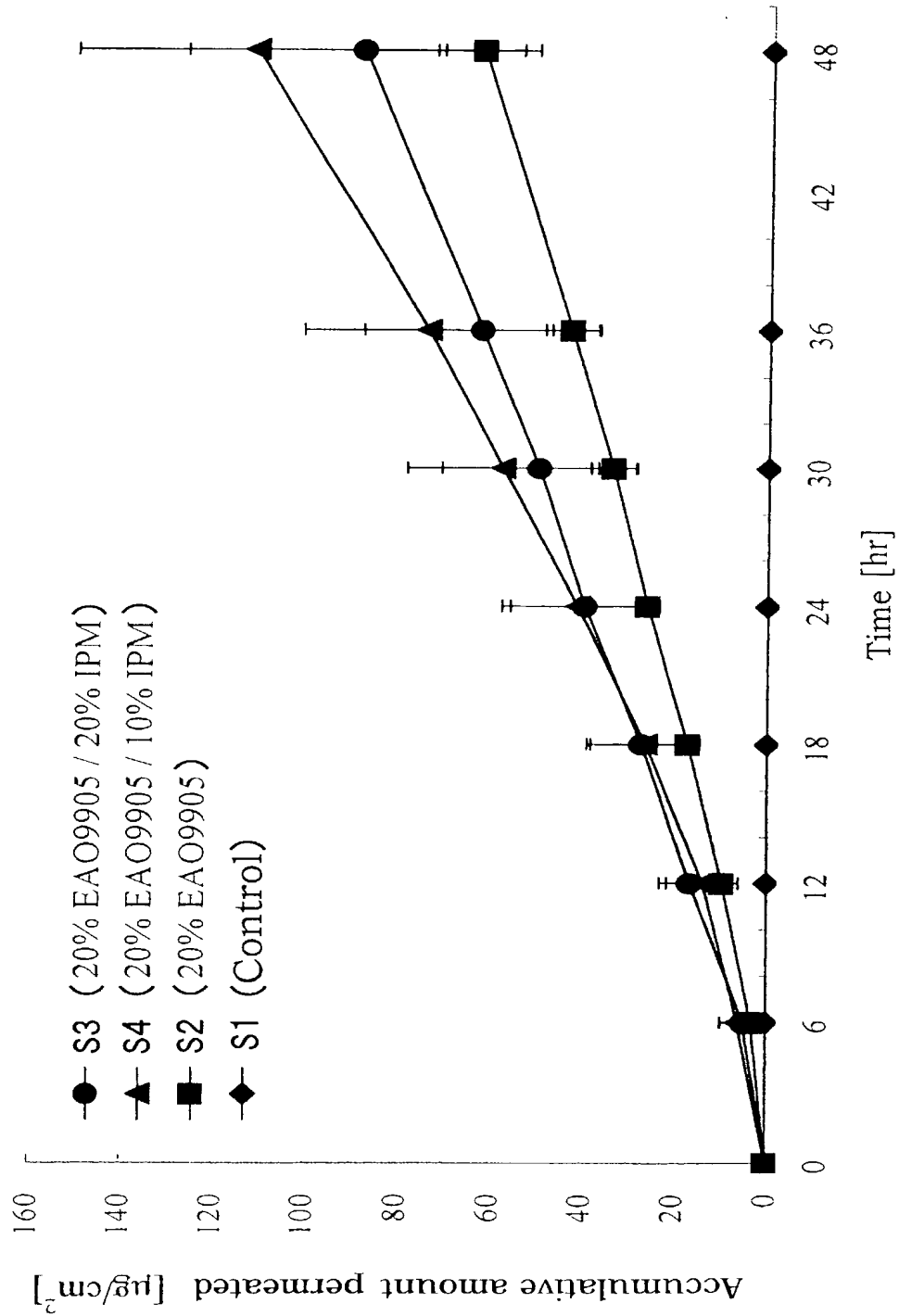


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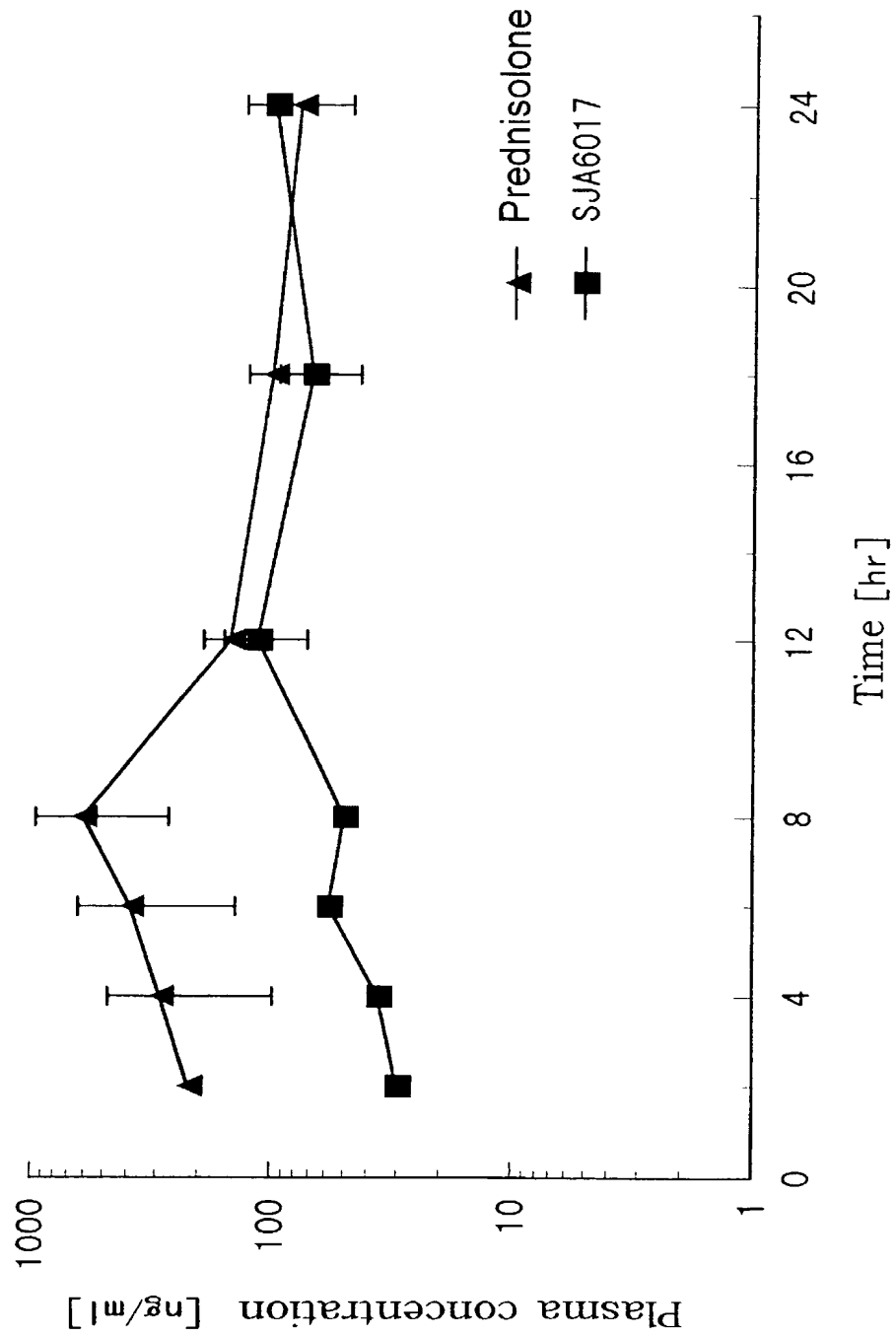


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Inventor: TOJO et al
Docket No.: 133574USWO

Title: OPHTHALMIC ADHESIVE PREPARATIONS FOR PERCUTANEOUS ABSORPTION

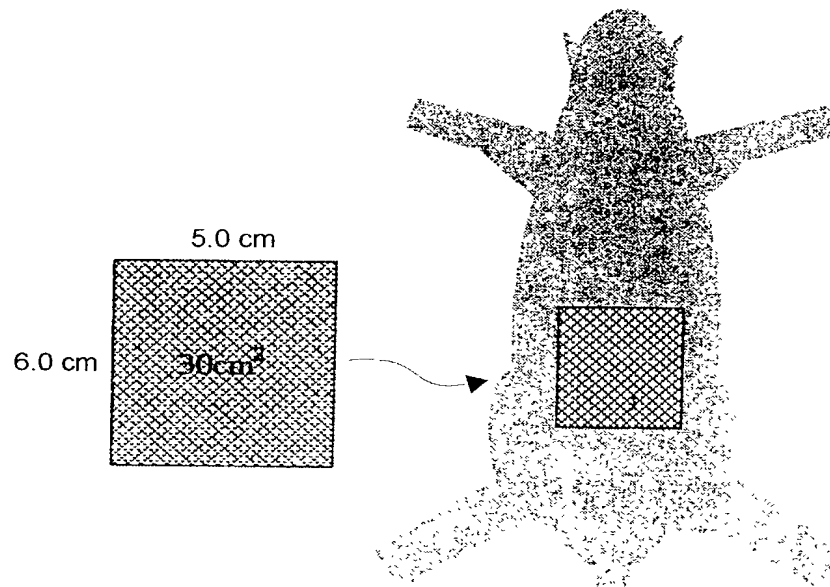
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Sheet 7 of 7

10/089431

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Merchant & Gould
United States Patent Application
COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that

I verily believe I am the original, first and sole inventor (if only one name is listed below) or a joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Insert TITLE of invention

OPHTHALMIC TRANSDERMAL PATCHES

Check a or b

The specification of which

a. ☐ is attached hereto

b. ☐ was filed on _____

If "b" checked, complete

as application serial no. _____

and was amended on _____ (if applicable)

If PCT Application

(in the case of PCT-filed application)

Insert Int. application
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described and claimed in international no. PCT/JP00/06815 filed 29 SEPTEMBER 2000

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I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a). (Reprinted on back side).

I hereby claim foreign priority benefits under Title 35, United States Code, § 119/365 of any foreign application(s) for patent of inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on the basis of which priority is claimed.

Prior applications
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a. ☐ no such applications have been filed.

b. ☒ such applications have been filed as follows:

FOREIGN APPLICATION(S), IF ANY, CLAIMING PRIORITY UNDER 35 USC § 119			
COUNTRY	APPLICATION NUMBER	DATE OF FILING (day, month, year)	DATE OF ISSUE (day, month, year)
Japan	291002/99	13, 10, 1999	
ALL FOREIGN APPLICATION(S), IF ANY, FILED BEFORE THE PRIORITY APPLICATION(S)			
COUNTRY	APPLICATION NUMBER	DATE OF FILING (day, month, year)	DATE OF ISSUE (day, month, year)

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I hereby claim the benefit under Title 35, United States Code, § 120/365 of any United States and PCT international application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

For Continuation-in-Part
(CIP) Applications, complete

U S APPLICATION NUMBER	DATE OF FILING (day, month, year)	STATUS (patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or patent agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith.

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Gorman, Alan G	Reg No 38,472	Prendergast, Paul	Reg No 46,068	Xu, Min S	Reg No 39,536
Gould, John D	Reg No 18,223	Pytel, Melissa J	Reg No 37,209	Zeuhl, Anthony R	Reg No 45,255

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Please direct all correspondence in this case to Merchant & Gould P.C at the address indicated below (or if no address is specified, the first address).

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Insert FULL name(s)
AND address(es) of
actual inventor(s)

2 0 1	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
2 0 2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP	
POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY	
2 0 3	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP	
POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY	
SIGNATURE OF INVENTOR 201		SIGNATURE OF INVENTOR 202		SIGNATURE OF INVENTOR 203
DATE		DATE		DATE

Each inventor must
sign & date

Note: No legalization or
other witness required

Revised 04/12/00

For Additional Inventors:

☐ Check box and attach sheet with same information, including date and signature.